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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/931,219	FALO ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-32,34-47,49-61 and 63-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-32,34-47,49-61 and 63-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 29-32, 34-47, 49-61, 63-112 remain pending and are under consideration in the instant office action.

This action is non-final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-32, 34-47, 49-61 and 63-112 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transfecting APCs with DNA encoding an antigen distributed on a particle surface using a gene gun by intradermal or subcutaneous injection, transfecting APCs of the skin and obtaining an immune response against the antigen, does not reasonably provide enablement for eliciting an immune response that destroys HIV infected cells using DNA encoding gp120 or gp160 as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Breadth of the claims

Claims 29, 44, 59, 68 and 71 encompass using DNA encoding an antigen to elicit an immune response against HIV proteins that destroys virally infected cells. Claims

41, 56, 92 and 108 specifically require using DNA encoding an antigen to elicit an immune response against HIV gp120 or gp160 that destroys virally infected cells.

State of the art and unpredictability of using gene delivery to treat disease

The state of the art at the time of filing was that the combination of vector, promoter, route of administration, level of expression and target tissue required to obtain a therapeutic or prophylactic effect using gene therapy was unpredictable. Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (pg 198, col. 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (pg 53, 1st ¶). Deonarain reviews new techniques under experimentation in the art that show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is

unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates, "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

State of the art and unpredictability of inducing an immune response capable of treating retroviral infection

The state of the art regarding treating retroviral infection was unpredictable. Stricker (Medical Hypotheses, June 1997, Vol. 48, pages 527-9) teaches that attempts to develop a vaccine against HIV have been unsuccessful because HIV vaccines do not neutralize HIV (pg 527, last paragraph through all of pg 528). Overall, a lack of understanding about protective immunity to HIV in humans, the sequence variability of HIV and the rapid replication of HIV contribute the ineffectiveness of vaccines against HIV (Bangham, Nov. 29, 1997, Lancet, Vol. 350, pages 1617-1621; page 1617, top of col. 1).

More specifically, Veljkovic (Vaccine, 2001, Vol. 19, pg 1855-1862) taught:

> "As was recently reported, the rgp120 subunit vaccine tested in HIV-negative individuals was not only not effective - participants in Phase I:II clinical vaccine trials who have become infected during or following immunization with the HIV-1 env had in their sera significant neutralizing antibody titers against vaccine isolates before they became infected [2,3] - but could also be dangerous [4]." (pg 1856, col. 1, first sentence of the second full paragraph)

Thus, the immune response against an HIV gp120 vaccine is inadequate to provide a prophylactic or therapeutic effect against HIV infection.

In fact, Veljkovic taught HIV can escape from immune control by HIV-specific

CTL recognizing a single epitope undergoes viral mutation and is favored when the CTL response is against one HIV epitope (pg 1857, col. 1, last sentence of the first full paragraph). McMichael explicitly described this phenomenon (Annual Rev. Immunol., 1997, Vol. 15, pg 271-296; see entire article).

Finally, Weber (Eur. J. Clin. Microbiol. Infect. Dis., Nov. 2001, Vol. 20, pg 800-803) described the phase I clinical trial using plasmid encoding HIV-1 gp160 to treat HIV-infected humans. "Even though both trials were designed as phase I clinical trials, with special focus on safety, preliminary data suggest that vaccination with the present HIV-1 DNA construct did not show any virological or immunological efficacy, which is in contrast to findings in the chimpanzee model" (pg 802, col. 2, first sentence of first full paragraph). Thus, plasmid DNA encoding gp160 does not have a therapeutic effect in humans and using DNA encoding HIV proteins in primate models does not correlate to expected results in humans.

Teachings in the specification

The specification suggests using DNA encoding HIV gp120 or gp160 to elicit an immune response against HIV gp120 or gp160 that destroys virally infected cells (pg 4, lines 22-26; pg 6, lines 1-7).

Rejection

Administering DNA encoding gp120 or gp160 to an individual does not elicit an anti-HIV immune response that destroys HIV infected cells as discussed in the art at the time of filing. Given the unpredictability in the art taken with the mere suggestion disclosed in the specification to use gp120 or gp160 in the claimed invention, applicants

fail to reasonably enable those of skill to elicit an immune response against gp120 or gp160 that destroys HIV infected cells using DNA encoding gp120 or gp160. Therefore, it would have required one of skill undue experimentation to elicit an immune response against gp120 or gp160 that destroys HIV infected cells using DNA encoding gp120 or gp160. Accordingly, the specification fails to enable those of skill to elicit an immune response against gp120 or gp160 that destroys HIV infected cells using DNA encoding gp120 or gp160 as claimed.

Claim Rejections - 35 USC § 102

Tang of record has been withdrawn because no evidence can be found to indicate the antibody response against human growth hormone (hGH) elicited by gene gun administration of DNA encoding hGH as taught by Tang would elicit an anti-tumor or anti-viral immune response in the host that destroys neoplastic or virally infected cells as claimed.

Barry (1994) of record has been withdrawn because no evidence can be found to indicate the antibody response against human growth hormone (hGH) elicited by gene gun administration of DNA encoding hGH as taught by Barry would elicit an anti-tumor or anti-viral immune response in the host that destroys neoplastic or virally infected cells as claimed.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 29, 68, 69, 72-74, 82, 84, 85, 95 and 100 are rejected under 35 U.S.C. 102(a) as being anticipated by Webster (Vaccine, Dec. 1994, Vol. 12, No. 16, pg 1495-1498) as supported by Robinson (Seminars in Immunology, 1997, Vol. 9, pg 271-283), Kuby (Immunology, 1992, W.H. Freeman and Company, New York, pg 208) and Peachman (Methods, 2003, Vol. 31, pg 232-242).

Webster taught administering DNA encoding the hemagglutinin glycoprotein (HA) of influenza to the skin of ferrets using the Accell electric discharge particle bombardment device (a gene gun). Gold beads having the DNA on the surface were administered to the skin of the ferrets (pg 1495, col. 1, DNA Vaccines; pg 1496, col. 1,

second full paragraph; pg 1496, col. 2, first sentence in the first full paragraph). Half of the beads were delivered to the epidermal layer, one-third were delivered to the stratum corneum and the remainder were delivered to the dermis (pg 1496, col. 1, second full paragraph, "Visual enumerations of the beads in these ferrets...").

The board's belief that "direct injection" and "particulate bombardment" are mutually exclusive (paragraph bridging pg 9-10 of the decision by the board 1-29-03) is in error. The two paragraphs in the specification discussing "particulate bombardment inoculations" and "direct injection" are not mutually exclusive because both paragraphs discuss and relate to "particulate DNA injections." The first paragraph on pg 6, lines 21-29, of the instant application discusses particulate bombardment inoculations and delivery of polynucleotides to APCs, while the second paragraph starting on pg 6, line 30 states "In another embodiment of the present invention a mammalian host is immunized with a particulate polynucleotide by direct injection including but not limited to subcutaneous injection, epidermal injection, dermal injection, lymphatic injection and intra venous injection." The second paragraph starting on pg 6, line 30, does not exclude using a particle bombardment to achieve "direct injection." Therefore, "direct injection," mentioned in the second paragraph does not exclude using the biolistic gene gun mentioned in the first paragraph for administration directly into the dermis or epidermis. In fact, applicants exemplify using particulate bombardment (gene gun) for subcutaneous injection, i.e. "direct injection," on pg 25, lines 25-27.

Thus, Webster injected DNA on particulate gold beads to the dermal layer of the skin using a gene gun, which meets the limitation of "direct injection."

The ferrets were challenged with influenza and were protected against infection (pg 1496, col. 2, first full paragraph), which is equivalent to an "anti-viral immune response in said host that destroys... ...virally infected cells."

APCs of the skin injected by Webster were inherently transfected with the DNA because i) administration of DNA to the skin using gold beads and a gene gun as taught by Webster is the same method used by applicants on pg 25, lines 20-22, ii) the HA protein was expressed in vivo as evidenced by an immune response against HA (pg 1496, Table 2), iii) the amount of DNA used by Webster was adequate to transfect numerous cells of the skin including APCs, and v) Peachman taught the gold particles used for gene gun delivery permeate plasma membranes, and therefore directly transfect a variety of cells in the skin, including Langerhans cells located in the stratum spinosum and dermal dendritic cells (pg 237, 2.1.2.1, specifically the third sentence of that section).

APCs of the skin injected by Webster inherently presented HA in an MHC-I manner such that an antiviral immune response occurred as claimed because i) Kuby taught "class I MHC molecules bind peptides derived from endogenous antigen synthesized within altered self cells (e.g., virus-infected cells)" (pg 208 "MHC and antigen presentation"), ii) the transfected cells of Webster are "altered self cells" as discussed in Kuby, iii) the step of administering DNA using an Accell gold bead gene gun described by Webster is the same step of administering DNA using an Accell gold bead gene gun described by applicants on pg 25, lines 20-25, and iv) Robinson taught

antigens synthesized and expressed in transfected cells enter pathways for both MHC I and MHC II (paragraph bridging pg 271-272; Table 1 "Raise both CTL and antibody").

Peachman, Kuby and Robinson are provided to support the examiner's inherency arguments and are not relied upon for the basis of the rejection.

Claims 29, 68, 69, 72-74, 82, 84, 85, 92, 95 and 100 are rejected under 35 U.S.C. 102(a) as being anticipated by Haynes (AIDS research and human retroviruses, 1994, Vol. 10, Supplement 2, pg S43-45) or Haynes (Vaccine, 1994, Cold Spring Harbor, Modern approaches to new vaccines including prevention of AIDS, pg 65-70), as supported by Robinson (Seminars in Immunology, 1997, Vol. 9, pg 271-283), Kuby (Immunology, 1992, W.H. Freeman and Company, New York, pg 208) and Peachman (Methods, 2003, Vol. 31, pg 232-242).

Haynes (AIDS research and human retroviruses, 1994, Vol. 10, Supplement 2, pg S43-S45) taught administering DNA encoding the gp120 protein of HIV to the skin induced an anti-gp120 cellular immune response (pg S44, col. 2, second full paragraph, "To this end, preliminary experiments demonstrated that splenocytes from animals that received HIV-1 gp120 epidermal DNA immunizations exhibited sifnificante levels of cytolytic activity recognizing syngeneic target cells pulsed with a gp120 v3 loop peptide... ...representing a known CTL epitope[8]." This sentence inherently refers to using the Accell electric discharge particle bombardment device (a gene gun) as described on pg S44, col. 1, in the first two paragraphs, because the only means of epidermal immunization described by Haynes is the Accell gene gun (see entire article),

because the fourth sentence of the paragraph describing the CTL response upon epidermal immunization refers to using voltage and because the second sentence of the abstract states Accell gene gun delivery resulted in "antigen expression in epidermal cells that stimulated induction of antigen specific humoral and cytotoxic cellular immune responses."

The board's belief that "direct injection" and "particulate bombardment" are mutually exclusive (paragraph bridging pg 9-10 of the decision by the board 1-29-03) is in error. The two paragraphs in the specification discussing "particulate bombardment inoculations" and "direct injection" are not mutually exclusive because both paragraphs discuss particulate DNA injections. The first paragraph on pg 6, lines 21-29, of the instant application discuss particulate bombardment inoculations and delivery of polynucleotides to APCs, while the second paragraph starting on pg 6, line 30 states "In another embodiment of the present invention a mammalian host is immunized with a particulate polynucleotide by direct injection including but not limited to subcutaneous injection, epidermal injection, dermal injection, lymphatic injection and intra venous injection." The second paragraph starting on pg 6, line 30, does not exclude using a particle bombardment to achieve "direct injection." Therefore, "direct injection" does not exclude using a biolistic gene gun for administration directly into the dermis or epidermis. In fact, applicants exemplify using particulate bombardment (gene gun) for subcutaneous injection, i.e. "direct injection," on pg 25, lines 25-27. Haynes injected DNA on particulate gold beads to the dermal layer of the skin using a gene gun, which meets the limitation of "direct injection."

The DNA of Haynes was inherently delivered to and expressed in dendritic cells of the epidermis and presented in a manner that elicited an immune response against the gp120 V3 loop because a CTL response against the gp120 V3 loop was obtained and because Peachman taught the gold particles used for gene gun delivery permeate plasma membranes, and therefore directly transfect a variety of cells in the skin, including Langerhans cells located in the stratum spinosum and dermal dendritic cells (pg 237, 2.1.2.1, specifically the third sentence of that section).

The gp120 V3 loop peptide expressed by Haynes is inherently expressed in an MHC-I pathway as claimed because i) reference 8 cited by Haynes in the first full paragraph of column 2 on pg S44 teaches the gp120 V3 loop peptide is only recognized in an MHC-I manner (pg S45, Reference 8, Takahashi "An immunodominant epitope of the human immunodeficiency virus envelope glycoprotein gp160 recognized by class I major histocompatibility complex molecule-restricted murine cytotoxic T lymphocytes"), ii) Kuby (Immunology, 1992, W.H. Freeman and Company, New York) taught "class I MHC molecules bind peptides derived from endogenous antigen synthesized within altered self cells (e.g., virus-infected cells)" (pg 208 "MHC and antigen presentation"), iii) the transfected cells of Haynes are "altered self cells" as discussed in Kuby, iv) the method used by Haynes is the same as the method described by applicants on pg 25, lines 20-22, and v) Robinson taught antigens synthesized and expressed in transfected cells enter pathways for both MHC I and MHC II (paragraph bridging pg 271-272; Table 1 "Raise both CTL and antibody").

Peachman, Kuby and Robinson are provided to support the examiner's inherency arguments and are not relied upon for the basis of the rejection.

Haynes (Vaccine, 1994) has the same disclosure.

Haynes (AIDS Res. Human Retrovirus, 1994) was available March 1995 on STN.

Haynes (Vaccine, 1994) was available Oct. 3, 1994 on STN.

Claims 29, 68, 69, 72-74, 82, 84, 85, 92, 95 and 100 are rejected under 35 U.S.C. 102(b) as being anticipated by the abstract presented by Haynes at the 11th annual meeting on modern approaches to new vaccines in September 1993 as supported by Robinson (Seminars in Immunology, 1997, Vol. 9, pg 271-283), Kuby (Immunology, 1992, W.H. Freeman and Company, New York, pg 208) and Peachman (Methods, 2003, Vol. 31, pg 232-242).

Without evidence to the contrary, the abstract in Haynes (Vaccine, 1994) and Haynes (AIDS Res. Human Retrovirus, 1994) was presented and available to the public at the annual meeting on modern approaches to new vaccines in September 1993. Therefore, the claims are also being rejected under 102(b) using the same abstract and reasoning in the rejection above.

Claims 29, 68, 69, 72-74, 82, 84, 85, 95 and 100 are rejected under 35 U.S.C. 102(a) as being anticipated by Lai (DNA and cell biology, July 1995, Vol. 14, No. 7, pg 643-651) as supported by Robinson (Seminars in Immunology, 1997, Vol. 9, pg

271-283), Kuby (Immunology, 1992, W.H. Freeman and Company, New York, pg 208) and Peachman (Methods, 2003, Vol. 31, pg 232-242).

Lai taught administering DNA encoding a mycoplasma antigen to the skin induced an anti-mycoplasma protective immune response. The DNA was distributed on a gold particle surface and delivered to the skin using a gene gun (pg 645, paragraph bridging column 1-2; pg 646, "Inoculation with plasmid DNA induces humoral immunity;" pg 647, "Plasmid DNA induces cell-mediated immunity" and pg 648, "Evaluation of vaccine efficacy").

The board's belief that "direct injection" and "particulate bombardment" are mutually exclusive (paragraph bridging pg 9-10 of the decision by the board 1-29-03) is in error. The two paragraphs in the specification discussing "particulate bombardment inoculations" and "direct injection" are not mutually exclusive because both paragraphs discuss particulate DNA injections. The first paragraph on pg 6, lines 21-29, of the instant application discuss particulate bombardment inoculations and delivery of polynucleotides to APCs, while the second paragraph starting on pg 6, line 30 states "In another embodiment of the present invention a mammalian host is immunized with a particulate polynucleotide by direct injection including but not limited to subcutaneous injection, epidermal injection, dermal injection, lymphatic injection and intra venous injection." The second paragraph starting on pg 6, line 30, does not exclude using a particle bombardment to achieve "direct injection." Therefore, "direct injection" does not exclude using a biolistic gene gun for administration directly into the dermis or epidermis. In fact, applicants exemplify using particulate bombardment (gene gun) for

subcutaneous injection, i.e. "direct injection," on pg 25, lines 25-27. Thus, Lai injected DNA on particulate gold beads to the dermal layer of the skin using a gene gun, which meets the limitation of "direct injection."

APCs of the skin injected by Lai were inherently transfected with the DNA because i) administration of DNA to the skin using gold beads and a gene gun as taught by Lai is the same method used by applicants on pg 25, lines 20-22, ii) mycoplasma proteins were expressed in vivo as evidenced by an cellular immune response against mycoplasma proteins (pg 648, Table 1), iii) the amount of DNA used by Lai was adequate to transfect numerous cells of the skin including APCs, and v) Peachman taught the gold particles used for gene gun delivery permeate plasma membranes, and therefore directly transfect a variety of cells in the skin, including Langerhans cells located in the stratum spinosum and dermal dendritic cells (pg 237, 2.1.2.1, specifically the third sentence of that section).

APCs of the skin injected by Lai inherently presented HA in an MHC-I manner such that an antiviral immune response occurred because i) Kuby taught "class I MHC molecules bind peptides derived from endogenous antigen synthesized within altered self cells (e.g., virus-infected cells)" (pg 208 "MHC and antigen presentation"), ii) the transfected cells of Lai are "altered self cells" as discussed in Kuby, iii) the step of administering DNA using an Accell gold bead gene gun described by Lai is the same as administering DNA using an Accell gold bead gene gun described by applicants on pg 25, lines 20-25, and iv) Robinson taught antigens synthesized and expressed in

transfected cells enter pathways for both MHC I and MHC II (paragraph bridging pg 271-272; Table 1 "Raise both CTL and antibody").

Peachman, Kuby and Robinson are provided to support the examiner's inherency arguments and are not relied upon for the basis of the rejection.

Claims 29, 68, 69, 71, 72, 74, 82, 84, 98, and 100 are rejected under 35 U.S.C. 102(b) as being anticipated by Hui (J. Immunological Methods, May 16, 1994, Vol. 171, pg 147-155) as supported by Robinson (Seminars in Immunology, 1997, Vol. 9, pg 271-283) and Kuby (Immunology, 1992, W.H. Freeman and Company, New York, pg 208).

Hui administered DNA encoding a H-2Kb antigen directly to the thigh or spleen using a microparticles and a gene gun (pg 148, 2.2 DNA Construct, 2.4 Microprojectile bombardment; pg 149, 2.5 Genetic Immunization, second half of paragraph). The DNA induced an anti-H-2Kb cellular immune response that destroyed tumor cells in vitro (pg 151, 3.1 "Induction of anti-H-2Kb CTL; 3.2 "Time course of expression of the H-2Kb molecules..."; Table 1). H-2Kb is a tumor antigen because it is expressed on EL-4 tumors and recognized in CTL assays (caption of Table 1 on pg 51).

The board's belief that "direct injection" and "particulate bombardment" are mutually exclusive (paragraph bridging pg 9-10 of the decision by the board 1-29-03) is in error. The two paragraphs in the specification discussing "particulate bombardment inoculations" and "direct injection" are not mutually exclusive because both paragraphs discuss particulate DNA injections. The first paragraph on pg 6, lines 21-29, of the

instant application discuss particulate bombardment inoculations and delivery of polynucleotides to APCs, while the second paragraph starting on pg 6, line 30 states "In another embodiment of the present invention a mammalian host is immunized with a particulate polynucleotide by direct injection including but not limited to subcutaneous injection, epidermal injection, dermal injection, lymphatic injection and intra venous injection." The second paragraph starting on pg 6, line 30, does not exclude using a particle bombardment to achieve "direct injection." Therefore, "direct injection" does not exclude using a biolistic gene gun for administration directly into the dermis or epidermis. In fact, applicants exemplify using particulate bombardment (gene gun) for subcutaneous injection, i.e. "direct injection," on pg 25, lines 25-27. Thus, Hui injected DNA on particulate gold beads to the thigh and spleen using a gene gun, which meets the limitations of "direct injection" and distributing DNA on particle surface as claimed.

APCs of the thigh and spleen described by Hui were inherently transfected with the DNA because i) H-2Kb proteins were expressed in vivo as evidenced by a cellular immune response against H-2Kb proteins (pg 151, Section 3.1), ii) the cellular immune response could not occur without H-2Kb presentation in an APC, iii) the amount of DNA used by Hui was adequate to transfect numerous cells of the thigh and spleen including APCs.

APCs of the skin injected by Hui inherently presented H-2Kb in an MHC-I manner such that an anti-tumor immune response occurred because i) Kuby taught "class I MHC molecules bind peptides derived from endogenous antigen synthesized within altered self cells (e.g., virus-infected cells)" (pg 208 "MHC and antigen presentation"), ii)

the transfected cells of Hui are "altered self cells" as discussed in Kuby, iii) Robinson taught antigens synthesized and expressed in transfected cells enter pathways for both MHC I and MHC II (paragraph bridging pg 271-272; Table 1 "Raise both CTL and antibody").

Kuby and Robinson are provided to support the examiner's inherency arguments and are not relied upon for the basis of the rejection.

Contrary to the board's decision on pg 13, a 3-4 fold increase in CTL response against H-2Kb after restimulation of splenocytes isolated from mice and stimulated with H-2Kb in vitro is an indication that an anti-H-2Kb immune response occurred in vivo. The splenocytes of test mice were compared those of wild-type mice and found to be different after stimulation with H-2Kb in vitro. More splenocytes in the test mice recognized H-2Kb than those of wild-type mice after H-2Kb stimulation in vitro; therefore, an immune response must have occurred in the test mice in vivo against H-2Kb that did not occur in wild-type mice. The lack of primary anti-H-2Kb CTL activity followed by detection of anti-H-2Kb CTL activity after restimulation in vitro on pg 151, section 3.1 is merely an indication that the initial test was not sensitive enough to detect the increased number of splenocytes that recognized H-2Kb. Restimulation in vitro is common practice when performing CTL assays to increase and expand the number of preexisting splenocytes that recognized H-2Kb; restimulation in vitro was performed on both splenocytes from test mice and wild-type mice and does not negate the fact that an immune response against H-2Kb occurred in vivo. The production of increased numbers of splenocytes that recognized H-2Kb in tumor cells after restimulation in vitro

as compared to non-transfected splenocytes also restimulated in vitro is an indication that increased numbers of splenocytes that recognized H-2Kb in tumors were present in the population of cells isolated from the transfected mouse, which is an anti-tumor immune response that destroys neoplastic cells as claimed.

Claims 29-32, 34, 40, 41, 44-47, 49, 55, 56, 59-61, 63, 68-85, 91 and 92 are rejected under 35 U.S.C. 102(e) as being anticipated by Weiner (US Patent 5,593,972) of record as supported by Peachman (Methods, 2003, Vol. 31, pg 232-242).

Weiner claims a method of immunizing an individual comprising: injecting into skeletal muscle tissue of said individual a DNA molecule that comprises a DNA sequence that encodes an antigen from a pathogen wherein said DNA molecule is expressed and an immune response is generated against said antigen. Weiner taught using DNA encoding gp160 of HIV (col. 27, line 51, through col. 28, line 5) or Her2/neu (col. 37, Example 25, lines 23-33; col. 38, line 66, through col. 39, line 22, claim 7). Other routes of administration include intradermal and subcutaneous injection by means including needleless injection devices or "microprojectile bombardment gene guns" (col. 9, lines 42-52; col. 16, line 62, through col. 17, line 18). Weiner specifically taught direct injection by biolistic gene gun and gold particles in col. 20, lines 32-36. In fact, Weiner taught increased efficiency of the immune response as compared to intramuscular injection can be achieved by direct DNA delivery by particle bombardment (col. 32, lines 55-57).

The immune response obtained by Weiner produced a CTL response that eliminated tumors expressing antigens (col. 27, lines 30-35; col. 33, lines 8-15 (gp160); col. 39, lines 14-22 (Neu)).

Weiner taught administering the vaccine to the individual *ex vivo* into removed cells of the individual, which are implanted after administering (col. 8, line 18-25; col. 16, line 62, through col. 17, line 18).

Weiner taught the antigens produced in the target cells are processed intracellularly: broken down into small peptides and bound by Class I MHC molecules and expressed on the cell surface (col. 8, line 37-51). Here, Weiner is describing antigen presentation; therefore, the cell being described by Weiner must be an antigen presenting cell as claimed. In fact, intradermal injection using gold particles and a biolistic gene gun as described by Weiner inherently transfects Langerhans cells (a type of dendritic cell) because i) administration of DNA to the skin using gold beads and a gene gun as taught by Weiner is the same method used by applicants on pg 25, lines 20-22, ii) the proteins encoded by the DNA were expressed in vivo as evidenced by a cellular immune response against the tumor (col. 27, lines 30-35), iii) Peachman taught the gold particles used for gene gun delivery permeate plasma membranes, and therefore directly transfect a variety of cells in the skin, including Langerhans cells located in the stratum spinosum and dermal dendritic cells (pg 237, 2.1.2.1, specifically the third sentence of that section).

The board's belief that "direct injection" and "particulate bombardment" are mutually exclusive (paragraph bridging pg 9-10 of the decision by the board 1-29-03) is

in error. The two paragraphs in the specification discussing "particulate bombardment inoculations" and "direct injection" are not mutually exclusive because both paragraphs discuss particulate DNA injections. The first paragraph on pg 6, lines 21-29, of the instant application discuss particulate bombardment inoculations and delivery of polynucleotides to APCs, while the second paragraph starting on pg 6, line 30 states "In another embodiment of the present invention a mammalian host is immunized with a particulate polynucleotide by direct injection including but not limited to subcutaneous injection, epidermal injection, dermal injection, lymphatic injection and intra venous injection." The second paragraph starting on pg 6, line 30, does not exclude using a particle bombardment to achieve "direct injection." Therefore, "direct injection" does not exclude using a biolistic gene gun for administration directly into the dermis or epidermis. In fact, applicants exemplify using particulate bombardment (gene gun) for subcutaneous injection, i.e. "direct injection," on pg 25, lines 25-27. Weiner taught injecting DNA on particulate gold beads using a gene gun and intradermal or subcutaneous delivery, which meets the limitations of "direct injection" and distributing DNA on particle surface as claimed.

Double Patenting

The double patenting rejection of claims 29-32, 34-47, 49-61 and 63-112 over U. S. Patent Application No. 09/967,956 has been withdrawn because the application has been abandoned.

The following prior art is made of record and is considered pertinent to applicant's disclosure:

For a description of how to deliver gold particles coated with DNA using the Accell gene gun, refer to Johnston (Methods in cell Biology, 1994, Vol. 43, Chapt, 14, pg 353-365) on pg 357, section A.2. Johnston describes transfecting macrophages in vitro (pg 360, 2nd full paragraph, (J774).

Shiver (Advanced Drug Delivery Rev., 1996, Vol. 21, pg 19-31) describes the humoral and cellular immunities elicited by HIV and influenza DNA vaccines. "Vaccines comprised of plasmid DNA constructs providing expression of cDNA-encoded antigens elicit potent humoral and cellular immunities in animals including major histocompatibility complex (MHC) I-restricted cytotoxic T lymphocytes (CTL) responses" (first line of abstract).

For further evidence that gold particle delivery of DNA encoding antigens to the skin by dermal injection causes transfection of dendritic cells and antigen presentation please see Larregina (Gene Therapy, 2001, Vol. 8, pg 608-617).

For further evidence that gold particle delivery of DNA encoding antigens to the skin by dermal injection causes transfection of dendritic cells, antigen presentation and humoral and cellular immune responses, please see Tuting (J. Invest. Dermatol., 1998, Vol. 111, pg 183-188).

For a diagram of the skin see the Dorlands Medical Dictionary page showing the cross section of the skin.

For evidence that Langerhans cells are a type of dendritic cell see the Dorlands Medical Dictionary definition of Langerhans cells.

For another reference teaching delivery of DNA encoding gp120 to the skin using the Accell gene gun, see Fuller (AIDS Research and Human Retroviruses, Nov. 1994, Vol. 10, No. 11, pg 1433-1441).

This office action is non-final.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

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